Dear author,

Please note that changes made in the online proofing system will be added to the article before publication but are not reflected in this PDF.

We also ask that this file not be used for submitting corrections.

Note: These proofs may contain color figures. Those figures may print black and white in the final printed book if a color print product has not been planned. The color figures will appear in color in all electronic versions of this book.

AUTHOR QUERY FORM

ELSEVIER	Book: Hoffer-1631503 Chapter: CH022	Please e-mail your responses and any corrections to: E-mail: a.sambamoorthy@elsevier.com

Dear Author,

Any queries or remarks that have arisen during the processing of your manuscript are listed below and are highlighted by flags in the proof. (AU indicates author queries; ED indicates editor queries; and TS/TY indicates typesetter queries.) Please check your proof carefully and answer all AU queries. Mark all corrections and query answers at the appropriate place in the proof using on-screen annotation in the PDF file. For a written tutorial on how to annotate PDFs, click https://www.elsevier.com/ data/assets/pdf_file/0004/475249/Annotating-PDFs-Adobe-Reader-9-X-or-XI.pdf. A video tutorial is also available at http://www.screencast.com/t/9OIDFhihgE9a. Alternatively, you may compile them in a separate list and tick off below to indicate that you have answered the query.

Please return your input as instructed by the project manager.

Uncited references: References that occur in the reference list but are not cited in the text. Please position each reference in the text or delete it from the reference list.		
Missing references: References listed below were noted in the text but are missing from the reference list. Please make the reference list complete or remove the references from the text.		
Location in Article	Query / remark	
AU:1, Page 1	Please check the edit made to the chapter title.	☐
AU:2, Page 1	Please provide the affiliation details for the authors.	☐
AU:3, Page 13	Please provide an abstract and keywords.	☐
AU:4, Page 1	Please check the hierarchy of the section headings.	☐
AU:5, Page 3	Please suggest if “normal” can be changed to “mild” in the sentence “Table 22.1 shows published results of…”.	☐
AU:6, Page 6	Please check if “versional” is correct.	☐
AU:7, Page 7	Please provide reference for “more recently”.	☐
AU:8, Page 10	Please update the volume number and page range for Ref. [29].	☐
AU:9, Page 4	The bold has been retained for the data in Table 22.1. Please check.	☐
AU:10, Page 4	The long dashes have been changed to N-dash. Please confirm.	☐

CHAPTER

c0022 22

Emerging Technologies for Diagnosing Mild Traumatic Brain Injury AU:1

Carey Balaban, Kurt Yankaskas and Alex Kiderman AU:2

OVERVIEW AND INTRODUCTION

s0010 AU:4

p0010 Mild traumatic brain injury (mTBI) has proven to be challenging to document objectively.[1] In the presence of a documented traumatic event (blunt trauma, acceleration deceleration, or blast energy exposure), it is defined primarily by the presence and persistence of symptoms that include difficulty thinking clearly, feeling slowed down, difficulty concentrating, difficulty remembering new information, headache, "pressure in the head", neck pain, feeling slowed down or like "in a fog," difficulty concentrating or remembering, confusion and/or drowsiness, fuzzy or blurry vision, nausea or vomiting (acutely), dizziness, sensitivity to light or noise, balance problems, feeling tired or having no energy, irritability, sadness, increased emotional lability, nervousness or anxiety, sleep disruptions (too much or too little), and trouble falling asleep.

p0015 By definition, there was, at worst, only a momentary change in conscious and there are no structural imaging findings showing intracranial injury. Emerging technologies, then, are needed to document functional deficits that are associated with the status of symptoms and objective clinical signs during acute, subacute, and chronic periods after injury.

p0020 Technologies for objective diagnosis of mTBI face several challenges. A first challenge is a clear differentiation between the empiricist approach of "finding markers" and the neuroscientific, precision-medicine goal of differentially diagnosing the biological bases for the underlying impairments. Even empirical biomarkers for "dinged and not quite right" need to be understood in terms of sites and mechanisms related to the injury and biological attempts to recover. Hence, is also essential that a selective and specific test battery is used to help identify the nature of the injury and track the clinical course in subacute and chronic post-injury periods in what is likely a very heterogeneous group. Are there specific and sensitive findings for injury that are nonlocalizing? Are there specific and sensitive localizing tests to refine a diagnosis? Are there specific and sensitive findings to document resolution of the symptoms and, more importantly, to indicate readiness for

DOI: https://doi.org/10.1016/B978-0-12-812344-7.00022-4

partial, or complete, return to normal activities? One incontrovertible consideration, though, is that evidence of delivery of energy to the head remains a necessary contextual criterion for diagnosis of mTBI.

p0025 A second challenge is to transcend the temptation to limit testing to familiar contemporary technologies. For example, harmonic sinusoidal oscillation testing of the horizontal vestibulo-ocular reflex or an audiogram may be of limited utility as a specific tool for mTBI testing. Rather, one must consider developing assessment technologies that can illuminate the sources of symptoms and signs that: (1) appear spontaneously; (2) can resolve or transform over time; and (3) can be elicited by dynamic test challenges.

p0030 A third challenge is to design technologies that provide rapid, selective, and specific identification of individual patients as having definitive mTBI. This standard requires a test battery to clearly distinguish the affected individuals as outliers from the population termed unaffected, normal, or subclinical. Pragmatically, the test will distinguish affected from unaffected individuals with a history of energy delivery to the head. This level of performance is a persistent "devil in the detail" for emerging technologies; it is a far more rigorous standard than simply showing a significant difference between partially overlapping groups of positive and negative subjects. Adherence to this standard drives the technology development process beyond the mechanical empiricism of enumerating similarities and differences between presentations by markers. Rather, the biologic bases behind specific and sensitive become important clues for making scientific sense of the clinical status of affected individuals.

p0035 A fourth challenge is to disentangle the neurosensory consequences of cognition and cognitive effects of neurosensory processing deficits. For example, there are strong interactive comorbidities between balance dysfunction and anxiety,[2,3] and interactions between vestibular dysfunction and cognitive performance.[4] This is manifested more widely in concussion by potential interactions between comorbid sequelae of balance and other neurosensory deficits, psychiatric signs and symptoms, personality features, and cognitive signs and symptoms. This vexing issue was noted more than a decade ago when Moore et al.[5] called for a concerted effort to move concussion from categorical classification to dimensional conceptualization. It was reiterated by Hoge et al.[6] in reference to veterans with mTBI. The prevailing view has been to assess, as independent domains, neurocognitive function, self-reported symptoms, and postural (or balance) control.[7]

p0040 The tendency to somaticize appears to be associated with a prolonged recovery from a concussion (defined by symptom reporting).[8,9] Path analysis suggested that somatization has an influence postconcussive recovery by influencing symptom expression.[8] Common sense appears to dictate that controls for propensity to self-report symptoms (and their persistence) need to be considered as part of any new assessment tools.

s0015 OBJECTIVE DIAGNOSTIC TECHNOLOGIES

s0020 Neurocognitive Tests and Symptom Inventories

p0045 The basic instruments for neurocognitive tests and symptom inventories are described in detail in a recent report of the IOM and NRC[10] and were reviewed comprehensively by

Hoffer-1631503 978-0-12-812344-7 00022

Arrieux et al.[11] These tests[7,12,13] include the Intermediate Post-Concussion Assessment and Cognitive Test (ImPACT®), King-Devick Test, Automated Neuropsychological Assessment Metrics (ANAM), Sport Concussion Assessment Tool (currently fifth edition, or SCAT5) and new products such as BrainCheck.[14] They can be administered automatically on electronic devices (computer, tablet, or personal digital device). The neurocognitive or neuropsychological components require baseline testing and typically include timed performance assessments inspired by the classic Trail-Making Tests.[15,16] The anecdotal reports that athletes who "low ball" their baseline performance reveal an inherent problem with operational use of these tests.

Symptom Inventories

The Post-Concussion Symptom Scale (PCSS, 25 items)[17] and the Sport Concussion Assessment Tool (5th edition, 22 items) symptom evaluation scale[18] are validated tools in common use. They elicit the seven-point Likert scale responses to describe the severity of similar lists of symptoms (Table 22.1). The scales are used to generate global symptom scores as a proxy for impairment. Because symptom perceptions can be affected by comorbid psychiatric, emotional, and personality features,[19,20] it is important to focus on instruments that can assess somatization[8,9] and relevant psychological and psychiatric features, such as the Minnesota Multiphasic Personality Inventory®-2 and Beck Depression Inventory.[20,21] Other validated instruments are useful to examine the perceived impact of specific symptoms on activities and quality of life. For example, the Dizziness Handicap Inventory is a validated, 25-item instrument that uses a three-point ordinal scale to express the attribution of symptoms and perceived handicaps to dizziness.[22-27] Hence, it is not surprising that DHI scores (and scores) showed reasonably strong positive correlation with responses to dizziness and mild cognitive impairment related items on the SCAT symptom inventory.[28] Other tests of the functional impact of symptoms, such as the Headache Impact Test (HIT-6t), are worthy of consideration for gauging impairment and improvement. A more general approach is represented by the recent efforts of the Patient-Reported Outcomes Information System (PROMIS) to develop a TBI Quality of Life (TBI-QOL) set of item banks focused on more severe forms of TBI.[29,30] The development of quality-of-life items specifically tailored to acute, subacute, and chronic mTBI could be of considerable value for monitoring therapeutic outcomes and the assessment of readiness to return to normal activities.

Identification of symptom clusters and gender differences in symptom expression is one direction for a concerted effort to move from categorical classification to dimensional conceptualization of concussion, as called for more than a decade ago by Moore et al.[5] Dimensional reduction by principal component or factor analysis of self-reporting symptom questionnaires are an approach for identifying symptom items associated with similar underlying dimensions. Table 22.1 shows published results of reductions from two studies, both utilizing groups of normal and acute TBI subjects.[28,31] There are some strong similarities between the results, but also differences that may reflect differences in the items and the orders of common items on the two instruments. Factor analysis of PCSS responses, obtained within 7 days of injury, indicated a four-component solution after

AU:5

t0010 TABLE 22.1 Symptom Scales and Initial Identification of Symptom Dimensions or Clusters in mTBI

Symptom (Rated Item)	PCSS Position and (Cluster) From Factor Analysis	SCAT Position and (Cluster) From Principal Component Analysis
Headache	1 (CogMigFatig)	1 (PTHx-M)
Nausea	2 (CogMigFatig) (Somatic)	4 (Nauseated)
Vomiting	3 (Som)	
Balance problems	4 (CogMigFatig)/(Somatic)	7 *(Dizzy-MCog)*
Dizziness (spinning or moving sensation)	5 (CogMigFatig)/(Somatic)	5 *(Dizzy-MCog)*
Fatigue	7 (CogMigFatig)	15 (PTHx-M)
Trouble falling asleep	8 (Sleep)	22 *(Emotional Lability)*
Drowsiness	11 (CogMigFatig)	17 (PTHx-M)
Sensitivity to light	12 (CogMigFatig) (Som))	8 (PTHx-M)
Sensitivity to noise	13 (CogMigFatig)	9 (PTHx-M)
Irritability	14 (CogMigFatig)*(Affect)*	19 *(Emotional Lability)*
Sadness	15 *(Affect)*	20 *(Emotional Lability)*
Nervous/anxious	16 *(Affect)*	21 *(Emotional Lability)*
Feeling more emotional than usual	17 *(Affect)*	18 *(Emotional Lability)*
Feeling slowed down	19 (CogMigFatig)	10 (PTHx-M)
Feeling like "in a fog"	20 (CogMigFatig)	11 (Cervicogenic)
Difficulty concentrating	21 (CogMigFatig)	13 *(Dizzy-MCog)*
Difficulty remembering	22 (CogMigFatig)	14 *(Dizzy-MCog)*
Visual problems/blurred vision	23 (CogMigFatig) (Som)	6 *(Dizzy MCog)*
Other	24	
Lightheadedness	6	–
Sleeping more than usual	9 (CogMigFatig) (Sleep)	–
Sleeping less than usual	10 (Sleep)	–
Numbness or tingling	18 (Som)	–
"Pressure in head"	–	2 (PTHx-M)
Neck pain	–	3 (Cervicogenic)
"Don't feel right"	–	12 (PTHx-M)
Confusion	–	16 *(Dizzy-MCog)*

mTBI, a cognitive-migraine-fatigue (CogMigFatig) factor, an affective (Affect) factor, a somatic (Somatic) factor a sleep-related (Sleep) factor.[31] A principal component analysis of SCAT questionnaire within 6 days of injury, on the other hand, identified a posttraumatic headache/migraine (PTHx-M) cluster, a dizzy with mild cognitive impairment (Dizzy-MCog) cluster, an emotional lability cluster, a cervicogenic cluster and nausea.[28] Despite similar objective findings, female participants with mTBI showed higher scores than their male counterparts on the PTHx-M cluster, while males with mTBI reported higher scores on the Dizzy-MCog complex. These data motivate a deeper exploration of symptom dimensions in acute, subacute and chronic mTBI.

s0030 Resting Brain Network Activity

p0060 Structural imaging, including tractography,[32-34] is expected to yield negative findings for mTBI. However, network science and network functional imaging[35,36] have been proposed as promising approaches to measure objective changes in brain activity that underlie the signs and symptoms of mTBI. A first step has been examination of resting network activity from fMRI,[37] MEG,[38,39] and EEG[40-42] recordings from patients with mTBI. These studies suggest that there may be modifications in activity between the default mode network (posterior cingulate cortex, inferior parietal cortex, inferolateral temporal cortex, and ventral anterior cingulate cortex) and frontal cortex,[43] which overlaps with the executive network (dorsolateral prefrontal and anterior cingulate cortex). A more recent study indicates that there are frequency specific differences in regional amplitude coupling in mTBI patients as well as augmented slow wave activity.[44] However, the correlational evidence linking these resting activity measures to the degree of cognitive impairment,[43] changes in emotional regulation and the persistence of posttraumatic complaints[45] is not strong.

s0035 Tests of Sensory Evoked Brain Activity in Specific Networks

p0065 Stimulus-evoked EEG activity has been used standardly for clinical evaluation of neurosensory processing. Commonly used diagnostic tests include evaluation of visual and auditory evoked potentials, which are conducted in conjunction with perceptual tests (e.g., perimetry and audiograms) to provide a more comprehensive clinical picture. Specialized visual and auditory sensory evoked potentials studies have shown some promise in documenting mTBI.

s0040 *Auditory Processing*

p0070 Metrics associated with central auditory processing are a very promising emerging area for assessment of mTBI. A proportion of Individuals with chronic blast mTBI[46] and concussions from blunt trauma show abnormal results on tests of central auditory processing, which includes speech comprehension in noise.[46,47] A very interesting study has shown alterations in speech-evoked frequency-following responses (also called the auditory brainstem response to complex sounds, or cABR) in children who were tested during the subacute stage mTBI.[48] These findings motivate further development of objective metrics associated with processing and interpreting complex auditory information.

s0045 *Visual Evoked Potentials*

p0075 Chronic mTBI may show P100 latency delays (▪ 15%) or amplitude reductions, but normal ERPs.[49] Luminance affects latency and amplitude differentially in chronic mTBI patients versus controls.[50] It has also been shown that binasal occlusion and base-in prisms induce altered changes in patients with chronic mTBI (1-27 years prior to testing).[51] These findings motivate further development of objective measures of the effects of mTBI on brain activity associated with complex visual information processing.

s0050 Quantitative Neurologic, Neurotologic, and Neurophthalmologic Diagnosis

p0080 The documentation of abnormal versional and vergence eye movements after mTBI has been a focus of a considerable research interest for more than a decade.[52-61] Technologies that incorporate some of these published results are available commercially. Here, the focus is on considerations for further test development, including oculomotor tests that incorporate cognitive tasks. AU:6

p0085 The temporal resolution, spatial resolution, and processing algorithms for eye tracking are essential technical considerations for precise and reproducible eye movement assessment. For video-oculographic methods, sampling at a rate of at least 500 Hz appears to be necessary to assess rapid eye movement timing and trajectories[62-64]; eye position resolution and precision should be {1 degree of arc for horizontal, vertical and torsional deviations. For slower eye movements, lower sampling rates (e.g., 100 Hz) are adequate.

p0090 Commercially available, advanced, video-based binocular eye tracking with infrared illumination systems currently provide independent, real time measurements for each eye at rates up to 250 Hz for horizontal and vertical movements and at rates up to 100 Hz for torsional eye movements. Video techniques generally use dark pupil tracking with detection algorithms for either the pupil centroid or an assumption of the pupil as an ellipse. Advanced eye tracking software uses a symmetric mass center algorithm that is designed to provide more accurate measurements when the pupil area is partially occluded.

p0095 Anti-saccade and predictive saccade tasks are examples of oculomotor tests with an embedded task that have proven to be useful in detecting mTBI objectively.[52,54,65,66] Antisaccade task performance can be regarded as a core executive function of response inhibition.[67] An enhanced prosaccadic error rate in subjects with acute mTBI may suggest disruption of inhibitory networks that are critical for suppressing the prosaccade. The inhibitory contributions likely involve the frontal cortex, as well as output from substantia nigra and pars reticulata to the superior colliculus and thalamus.[67] Like other saccades, an antisaccade is thought to be programmed in the frontal cortex. The predictive saccade task, on the other hand, is related to networks controlling timing of movements guided by short-term memory cues, including crus I of the cerebellum, medal prefrontal cortex, posterior cingulate cortex, posterior insula, and parahippocampal gyrus.[68] Because reactive saccades differentially engage a network that is related to oculomotor execution,[68] reactive and predictive saccade performance has differential diagnostic value for objective detection of damaged cortical pathways.

p0100 Anomalous convergence eye movements have been described in TBI patients on the basis of qualitative and semiquantitative observations and quantitative oculographic

metrics.[55,57,58,61] Demonstrations of convergence insufficiency have typically focused on the range of effective responses to static endpoints (near and far targets).[55,57,58] The results of analyses of convergence performance with oculographic methods in a diverse group of TBI patients[61] suggest that dynamic assessment is a promising line of investigation for differential diagnosis.

p0105 Inspection of the consensual pupillary light reflex is a component of standard neurologic exams. More recently, commercially available pupillometers can record the time course of the pupillary constriction and subsequent dilation (relaxation) objectively. Metrics for performance have included the onset latency and dynamic assessments of the velocity and magnitude of the response. A recent review[69] provides a comprehensive characterization of the current state-of-the-art. It is suggested that a more parsimonious and mechanistically insightful analyses could emerge by estimating parameters of formal models of the dynamics of these responses[70-75] in mTBI patients and matched control groups. AU:7

p0110 The near response is a coordinated motor program of disconjugate eye movements, pupil size changes, and lens accommodation. The near triad movement[76] is a coordinated execution of convergent eye movements, pupillary constriction (miosis), and increased lens curvature to track an approaching object. Divergent eye movement, pupillary dilation, and decreased lens curvature occur while tracking a receding object. On-going studies suggest that mTBI can be detected through an examination of the coordination of eye and pupil movements during a binocular disparity tracking task.

p0115 Static and dynamic posturography have become standard tools in the assessment of balance disorders. Hence, they have been used for assessing postural control disorders in mTBI (see, e.g.,[77-79]). The method has been useful to document objectively acute, subacute, and chronic emergent and/or a persistent sign of mTBI is responses to step or sinusoidal perturbations of the substrate or visual surround. Notable areas for development are the expanded use of measures such as approximate or Shannon entropy[80-82] to characterize system performance and applying ternary pseudorandom perturbations[83] to rapidly measure the transfer function for postural control.

p0120 Gait analysis has also been applied to assess anomalous locomotion after mTBI. Earlier studies in patients with moderate TBI (grade II concussion) demonstrated the utility of dual task cognitive paradigms for revealing gait disorders,[84] which was consistent with the emerging picture of the utility of multiple task challenges for gait assessment in other neurological disorders.[85] Based upon this earlier literature, more recent studies show promising results with applying dual task paradigms in patients with mTBI.[86,87]

s0055 Autonomic Function

p0125 The exacerbation of symptoms of mTBI by exercise has motivated examination of changes in autonomic motor control after injury. The high frequency relative power of heart rate variability was reported to be reduced during physical exertion in patients with chronic mTBI.[88] In a small sample of athletes, approximate entropy (a measure of complexity of beat-to-beat variability) was depressed transiently in the acute period after mTBI.[89] It is of further interest that altered patterns of heart rate variability may be a component of (developing) comorbid conditions such as anxiety.[90]

s0060 Olfactory System Function

p0130 Olfactory dysfunction has been documented for some patients with mTBI after either blast-wave exposure[91,92] or blunt-trauma exposures.[93-95] The olfactory system is, in fact, positioned strategically as a sentinel for head injury. The direct exposure of the olfactory epithelium and nerves to ambient air within the nasal cavity confers vulnerability to blast waves, particulate debris, and aerosols from explosions. Bone transmission of energy from impact to the ethmoid bone is another source of potential trauma to the nerves. The olfactory bulb and nerves also play and important role in glymphatic drainage into the lymphatic system.[96] The relatively superficial location of the olfactory bulb, tracts, and piriform cortex also may confer vulnerability for impact to the skull.

p0135 Olfactory testing approaches include threshold or suprathreshold Identification tests with a standardized set of odorant stimuli (e.g., Sniffin' Stickst or the Alberta Smell Test).[97] Results from limited studies suggested efficacy in detecting acute mTBI,[93] and that olfactory test results may have some prognostic capability for detection of residual brain dysfunction in longer term, follow-up neurological examinations.[91] Similarly, it was reported that acute olfactory dysfunction may be associated with an elevated likelihood of adverse cognitive, neuropsychiatric, and functional outcomes during longer term follow-ups.[95] The current technologies have the advantage of simplicity, but the test-retest reliability is lower than for standard oculomotor and vestibular testing.[97] Further studies are clearly needed to explore the roles of olfactory tests in screening batteries.

s0065 Biochemical Markers

p0140 Considerable effort has been invested in identifying reliable blood or cerebrospinal biochemical markers for mTBI from among markers for moderate and severe injury, with no definitive outcomes.[98-100] To date, the most definitive finding may be that some biomarkers help acutely in detecting the potentially CT-positive individuals among those who appear to be mild clinically. For example, Sharma et al.[101] reported that blood levels of the gelatinase, matrix metalloproteinase-2, C-reactive protein, and creatinine kinase type B can help differentiate CT-positive from CT-negative patients from samples drawn at an average of 7-10 hours post-injury. Prognostic applications seem to be a promising direction for biomarker technology development.

s0070 FUTURE DIRECTIONS: TOWARD INTEGRATIVE PRECISION MEDICAL DIAGNOSIS

p0145 A review of the emerging technologies for detecting and monitoring the course of mTBI suggests that we are still at a very rudimentary stage for developing comprehensive, rational approaches that illuminate the underlying neurobiology of the condition. However, there are promising indications that a combination of refined symptom inventories, objective tests of higher order neurological and cognitive functions, and sentinel biomarker tests can be both diagnostic in the short-term for the severity of impairment and prognostic for the likelihood of subacute and chronic complications. We can now envision test systems

that integrate dual-tasking, virtual/augmented reality and accelerometer technologies for more challenging, and ecologically valid clinical testing. The same advanced test systems will doubtless see wide usage in the rehabilitation sciences, as well. A major caveat, though, is that the development of these precision technologies will require rigorous attention to patient stratification criteria and both temporal and functional milestones that are critical to monitoring the clinical course of the individual.

References

1. Arnold M, Bousser M, Fahrni G, et al. Vertebral artery dissection: presenting findings and predictors of outcome. *Stroke* 2006;37:2499-503.
2. Balaban CD, Jacob RG, Furman JM. Neurologic bases for comorbidity of balance disorders, anxiety disorders and migraine: neurotherapeutic implications. *Expert Rev Neurother* 2011;11:379-94.
3. Balaban CD, Thayer JF. Neurological bases for balance-anxiety links. *J Anxiety Disorders* 2001;15:53-79.
4. Smith PF. The vestibular system and cognition. *Curr Opin Neurol* 2017;30:84-9.
5. Moore EL, Terryberry-Spohr L, Hope DA. Mild traumatic brain injury and anxiety sequelae: a review of the literature. *Brain Injury* 2006;20:117-32.
6. Hoge CW, Goldberg HM, Castro CA. Care of war veterans with mild traumatic brain injury—flawed perspectives. *N Engl J Med* 2009;360:1588-91.
7. Brolio SP, Puetz TW. The effect of sport concussion on neurocognitive function, self-report symptoms and postural control: a meta-analysis. *Sports Med* 2008;38:53-67.
8. Nelson LD, Tarima S, LaRoche AA, et al. Preinjury somatization symptoms contribute to cliical recovery after sport-related concussion. *Neurology* 2016;86:1856-63.
9. Root JM, Zuckerbraun NS, Wang L, et al. History of somatization is associated with prolonged recovery from concussion. *J Pediatr* 2016;174:139-44.
10. Graham R, Rivara FP, Ford MA, Spicer CM. *Sports concussions in youth: improving the science, changing the culture. Council IoMaNR*. Washington, DC: National Academies Press (US); 2014.
11. Arrieux JP, Cole WR, Ahrens AP. A review of the validity of computerized neurocognitive assessment tools in mild traumatic brain injury assessment. *Concussion* 2017;2:CNC31.
12. Brolio SP, Macciocchi SN, Ferrara MS. Sensitivity of the concussion assessment battery. *Neurosurgery* 2007;60:1050-8.
13. Alsalaheen B, Stockdale K, Pechumer D, Broglio SP. Validity of the immediate post-concussion assessment and cognitive testing. *Sports Med* 2016;46:1487-501.
14. Yang S, Flores B, Magal R, et al. Diagnostic accuracy of tablet-based software for the detection of concussion. *PLoS One* 2017;12:e0179352.
15. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Motor Skills* 1958;8:271-6.
16. Tombaugh TN. Trail making test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol* 2004;19:203-14.
17. Collins MW, Iverson GL, Lovell MR, McKeag DB, Norwig J, Maroon J. On-field predictors of neuropsychological and symptom deficit following sports-related concussion. *Clin J Sports Med* 2003;13:222-9.
18. Echemendia RJ, Meeuwisse WH, McCrory P, et al. The sport concussion assessment tool, 5th edition: Background and rationale. *Br J Sports Med* 2017;51:848-50.
19. Ruff RM, Camenzuli L, Mueller J. Miserable minority: emotional risk factors that influence the outcome of a mild traumatic brain injury. *Brain Injury* 1996;10:551-66.
20. Mooney G, Speed J. The association between mild traumatic brain injury and psychiatric conditions. *Brain Injury* 2001;15:865-77.
21. Mooney G, Speed J, Sheppard S. Factors related to recovery after mild traumatic brain injury. *Brain Injury* 2005;19:975-87.
22. Asmundson GJG, Stein MB, Ireland D. A factor analytic study of the dizziness handicap inventory: does it assess phobi avoidance in vestibular referrals? *J Vestibular Res* 1999;9:63-8.

23. Jacobson GP, Newman WW. Tne development of the dizziness handicap inventory. *Arch Otolaryngol Head Neck Surg* 1990;116:424-7.
24. Perez N, Garmendia I, Garcia-Granero M, Martin E, Garcia-Tapia R. Factor analysis and correlation between Dizziness Handicap Inventory and dizziness characteristics and impact on quality of life scales. *Acta Oto-Laryngol* 2001;545(Suppl):145-54.
25. Tamber A-L, Wilhelmsen KT, Strand LI. Measurement properties of Dizziness Handicap Inventory by cross-sectional and longitudinal designs. *Health Quality Life Outcomes* 2009;7:101.
26. Vereeck L, Truijen S, Wuyts FL, Van De Heyning PH. Internal consistency and factor analysis of the Dutch version of the Dizziness Handicap Inventory. *Acta Oto-Laryngol* 2007;127:788-95.
27. Vereeck L, Truijen S, Wuyts FL, Van De Heyning PH. The Dizziness Handicap Inventory and its relationship with functional balance performance. *Otol Neurotol* 2008;28:87-93.
28. Hoffer ME, Szczupak M, Kiderman A, et al. Neurosensory symptom complexes after acute mild traumatic brain injury. *PLoS One* 2016;11:e0146039.
29. Sherer M, Poritz JMP, Tulsky DS, Kisala PA, Leon-Novelo L, Ngan E. Conceptual structure of health-related quality of life for persons with traumatic brain injury: confirmatory factor analysis of the TBI-QOL. *Arch Phys Med Rehabil* 2017. AU:8
30. Tulsky DS, Kisala PA, Victorson D, et al. TBI-QOL: development and calibration of item bankd to measure patient reported outcomes after traumatic brain injury. *J Head Trauma Rehabil* 2016;31:40-51.
31. Kontos AP, Elbin RJ, Schatz P, et al. A revised factor structure for the post-concussion symptom scale: baseline and postconcussion factors. *Am J Sports Med* 2012;40:2375-84.
32. Narayana PA, Yu X, Hasan KM, et al. Multi-modal MRI of mild traumatic brain injury. *NeuroImage: Clin* 2015;7:87-97.
33. Mohammadian M, Roine T, Hirvonen J, et al. High angular resolution diffusion-weighted imaging in mild traumatic brain injury. *NeuroImage: Clin* 2017;13:174-80.
34. Aoki Y, Inokuchi R. A voxel-based meta-analysis of diffusion tensor imaging in mild traumatic brain injury. *Neurosci Biobehav Rev* 2016;66:119-26.
35. Stam CJ. Modern network science of neurological disorders. *Nat Rev Neurosci* 2014;15:683-95.
36. Eierud C, Craddock RC, Fletcher S, et al. Neuroimaging after mild traumatic brain injury: review and meta-analysis. *NeuroImage: Clin* 2014;4:283-94.
37. Sharp DJ, Scott G, Leech R. Network dysfunction after traumatic brain injury. *Nat Rev Neurol* 2014;10: 156-66.
38. Tarapore PE, Findlay AM, LaHue SC, et al. Resting state magnetoencephalography functional connectivity in traumatic brain injury. *J Neurosurg* 2013;118:1306-16.
39. Vakorin VA, Doesburg SM, da Costa L, Pang JR, Taylor MJ. Detecting mild traumatic brain injury using resting state magnetoencephalographic connectivity. *PLoS Comput Biol* 2016;12:e1004914.
40. Nuwer MR, Hovda DA, Schrader LM, Vespa PM. Routine and quantitative EEG in mild traumatic brain injury. *Clin Neurophysiol* 2005;116:2001-25.
41. Arciniegas DB. Clinical electrophysiologic assessments and mild traumatic brain injury: state-of-the-science and implications for clinical practice. *Int J Psychophysiol* 2011;82:41-52.
42. Haneef Z, Levin HS, Frost JD, Mizrahi EM. Electroencephalography and quantitative electroencephalography in mild traumatic brain injury. *J Neurotrauma* 2013;30:653-6.
43. Mayer AE, Mannell MV, Ling J, Gasparovic C, Yeo RA. Functional connectivity in mild traumatic brain injury. *Human Brain Map* 2011;32:1825-35.
44. Dunkley BT, Da Costa L, Bethune A, et al. Low-frequency connectivity is associated with mild traumatic brain injury. *NeuroImage: Clin* 2015;7:611-21.
45. van der Horn HJ, Liemburg EJ, Scheenen ME, de Koning ME, Spikman JM, van der Naalt J. Graph analysis of functional brain networks in patients with mild traumatic brain injury. *PLoS One* 2017;12:e0171031.
46. Gallun FJ, Diedesch AC, Kubli LR, et al. Performance on tests of central auditory processing by individuals exposed to high-intensity blasts. *J Rehabil Res Develop* 2012;49:1005-24.
47. Hoover EC, Souza PE, Gallun FJ. Auditory and cognitive factors associated with speech-in-noise complaints following mild traumatic brain injury. *J Am Acad Audiol* 2017;28:325-39.
48. Kraus N, Thompson EC, Krizman J, Cook K, White-Schwoch T, LaBella CR. Auditory biological marker of concussion in children. *Sci Rep* 2016;6:39009.

49. Freede S, Hellerstein LF. Visual electrodiagnostic findings in mild traumatic brain injury. *Brain Injury* 1997;11:25-36.
50. Fimreite V, Cuiffreda KJ, Yadav NK. Effect of luminance on the visually-evoked potential in visually-normal individuals and in mTBI/concussion. *Brain Injury* 2015;29:1199-210.
51. Yadav NK, Ciuffreda KJ. Effect of binasal occlusion (BNO) and base-in prisms on the visual evoked potential (VEP) in mild traumatic brain injury (mTBI). *Brain Injury* 2014;28:1568-80.
52. Heitger MH, Anderson TJ, Jones RD, Dalrymple-Alford JC, Frampton CM, Ardagh MW. Eye movement and visuomotor arm movement deficits following mild closed head injury. *Brain* 2004;127:575-90.
53. Suh M, Kolster R, Sarkar R, McCandliss R, Ghajar J. Consortium CaNR. Deficits in predictive smooth pursuit after mild traumatic brain injury. *Neurosci Lett* 2006;401:108-13.
54. Heitger MH, Jones RD, McLeod AD, Snell DL, Frampton CM, Anderson TJ. Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability. *Brain* 2009;132:2850-70.
55. Thiagarajan P, Cuiffreda KJ, Ludlam DP. Vergence dysfunction in mild traumatic brain injury (mTBI): a review. *Ophthalmic Physiol Opt* 2011;31:456-68.
56. Capo-Aponte JE, Urosevich TG, Temme LA, Tarbett A, Sanghera NK. Visual dysfunctions and symptoms during the subacute stage of blast-induced mild traumatic brain injury. *Military Med* 2012;177:804-13.
57. Alvarez TL, Kim EH, Vicci VR, Dhar SK, Biswal BB, Barrett AM. Concurrent visual dysfunctions in convergence insufficiency with traumatic brain injury. *Optom Vis Sci* 2012;89:1740-51.
58. Mucha A, Collins MW, Elbin RJ, et al. A brief Vestibular/Ocular Motor Screening (VOMS) assessment to evaluate concussions: preliminary findings. *Am J Sports Med* 2014;42:2479-86.
59. Cifu DX, Wares JR, Hoke KW, Wetzel PA, Gitchel G, Carne W. Differential eye movements in mild traumatic brain injury versus normal controls. *J Head Trauma Rehabil* 2015;30:21-8.
60. Samadani U, Ritlop R, Reyes M, et al. Eye tracking detects disconjugate eye movements associated with structural traumatic brain injury and concussion. *J Neurotrauma* 2015;32:548-56.
61. Tyler CW, Likova LT, Mineff KN, Elsaid AM, Nicholas SC. Consequences of traumatic brain injury for human vergence dynamics. *Front Neurol* 2015;5:282.
62. McCamy MB, Otero-Millan J, Leigh J, et al. Simultaneous recordings of human microsaccades and drifts with a contemporary video eye tracker and the serach coil technique. *PLoS One* 2015;10:e0128428.
63. Houben MMJ, Goumans J, van der Steen J. Recording three dimenional eye movements: scleral search coils versus video oculography. *Invest Ophthalmol Vis Sci* 2006;47:179-87.
64. van der Geest JN, Frens MA. Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. *J Neuroxcience Methods* 2002;114:185-95.
65. Balaban CD, Hoffer ME, Szczupak M, et al. Oculomotor, vestibular, and reaction time tests in mild traumatic brain injury. *PLoS One* 2016;11:e162168.
66. Hoffer ME, Balaban CD, Szczupak M, et al. The use of oculomotor, vestibular, and reaction time tests to assess mild traumatic brain injury (mTBI) over time. *Laryngosc Invest Otolaryngol* 2017;2:157-65.
67. Munoz DP, Everling S. Look away: the anti-saccade task and the voluntary control of eye movement. *Nat Rev Neurosci* 2004;5:218-28.
68. Lee SM, Peltsch A, Kilmade M, et al. Neural correlates of predictive saccades. *J Cognitive Neurosci* 2016;28:1210-27.
69. Ciuffreda KJ, Joshi NR, Truong JQ. Understanding the effects of mild traumatic brain injury on the pupillary light reflex. *Concussion* 2017;2:CNC36.
70. Stark L, Sherman PM. A servoanalytic study of the consensual pupil reflex to light. *J Neurophysiol* 1957;20:17-26.
71. Sun F, Krenz WC, Stark LW. A systems model for pupil size effect. I. Transient data. *Biol Cybern* 1983;48:101-8.
72. Sun F, Tauchi P, Stark L. Dynamic pupillary response controlled by the pupil size effect. *Exp Neurol* 1983;82:313-24.
73. Krenz WC, Stark L. Systems model for pupil size effect. II. Feedback model. *Biol Cybern* 1985;51:391-7.
74. Schor CM. A dynamic model of cross-coupling between accommodation and convergence: simulations of step and frequency responses. *Optom Vis Sci* 1992;69:258-69.
75. Privitera CM, Stark LW. A binocular pupil model for simulation of relative afferent pupil defects and the swinging flashlight test. *Biol Cybern* 2006;94:215-24.

76. Leigh RJ, Zee DS. *The neurology of eye movements*. 4th ed. New York: Oxford University Press; 2006.
77. Guskiewicz KM, Ross SE, Marshall SW. Postural stability and neuropsychological deficits after concussion in collegiate athletes. *J Athletic Train* 2001;36:263-73.
78. Hoffer ME, Balaban CD, Gottschall KR, Balough BJ, Maddox MR, Penta JR. Blast exposure: vestibular consequences and associated characteristics. *Otol Neurotol* 2010;31:232-6.
79. Pan T, Liao K, Roenigk K, Daly JJ, Walker MF. Static and dynamic postural stability in veterans with combat-related mild traumatic brain injury. *Gait Post* 2015;42:550-7.
80. Buckley TA, Oldham JR, Caccese JB. Postural control deficits identify lingering post-concussion neurological deficits. *J Sport Health Sci* 2016;5:61-9.
81. Sosnoff JJ, Brolio SP, Shin S, Ferrara MS. Previous mild traumatic brain injury and postural conrol dynamics. *J Athletic Train* 2011;46:85-91.
82. Gao J, Hu J, Buckley TA, White K, Hass C. Shannon and Renyi entropies to classify effects of mild traumatic brain injury on postural sway. *PLoS One* 2011;6:e24446.
83. Peterka RJ. Sensorimotor integration in human postural control. *J Neurophysiol* 2002;88:1097-118.
84. Catena RD, van Donkelaar P, Chou L-S. Cognitive task effects on gait stability following concussion. *Exp Brain Res* 2007;176:23-31.
85. Yogev G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Movem Disord* 2008;23:329-472.
86. Fino PC. A preliminary study of longitudinal differences in local dynamic stability between recently concussed and healthy athletes during single and dual-task gait. *J Biomech* 2016;49:1983-8.
87. Howell DR, Osternig LR, Chou L-S. Single-task and dual-task tandem gait test performance after concussion. *J Sci Med Sport* 2017;20:622-6.
88. Abaji JP, Currier D, Moore RD, Ellemberg D. Persisting effects of concussion on heart rate variability during physical exertion. *J Neurotrauma* 2016;33:811-17.
89. La Fountaine MF, Hefferman KS, Gossett JD, Bauman WA, De Meersman RE. Transient suppression of heart rate complexity in concussed athletes. *Autonom Neurosci* 2009;148:101-3.
90. Liao K-H, Sung C-W, Chu S-F, et al. Reduced power spectra of heart rate variability are correlated with anxiety in patients with mild traumatic brain injury. *Psych Res* 2016;243:349-56.
91. Ruff RI, Ruff SS, Wang X-F. Headaches among Operation Iraqi Freedom/Operation Enduring Freedom veterans with mild traumatic brain injury associated with exposures to explosions. *J Rehabil Res Dev* 2008;45:941-52.
92. Xydakis MS, Mulligan LP, Smith AB, Chen CH, Lyon DM, Belllucio L. Olfactory impairment and traumatic brain injury in blast-injured combat troops: a cohort study. *Neurology* 2015;84:1559-67.
93. De Kruik JR, Leffers P, Menheere PPCA, Meerhoff S, Rutten J, Twijnstra A. Olfactory function after mild traumatic brain injury. *Brain Injury* 2003;17:73-8.
94. Proskynitopoulos PJ, Stippler M, Kasper EM. Post-traumatic anosmia in patients with mild traumatic brain injury (mTBI): a systematic and illustrated review. *Surg Neurol Int* 2016;7:S263-75.
95. Schofield PW, Moore TM, Gardner A. Traumatic brain injury and olfaction: a systematic review. *Front Neurol* 2014;5:5.
96. Jessen NA, Munk ASF, Lundgaard I. Nedergaard. The glymphatic system--a beginner's guide. *Neurochem Res* 2015;40:2583-99.
97. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' Sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chem Senses* 1997;22:39-52.
98. Zetterberg H, Smith DH, Blennow K. Biomarkers of mild traumatic brain injury in cerebrospinal fluid and blood. *Nat Rev Neurol* 2013;9:201-10.
99. Agoston DV, Shutes-David A, Peskind ER. Biofluid markers of traumatic brain injury. *Brain Injury* 2017;31:1195-203.
100. Peskind ER, Kraemer B, Zhang J. Biofluid biomarkers of mild traumatic brain injury: whither plasma tau. *AMA Neurol* 2015;72:1103-5.
101. Sharma R, Rosenberg A, Bennett ER, Laskowitz DT, Acheson SK. A blood-based biomarker panel to risk-stratify mild traumatic brain injury. *PloS One* 2017;12:e0173798.

NON-PRINT ITEM

Abstract AU:3

XXX

Keywords: XXX; XXX; XXX; XXX; XXX; XXX